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CSIRO PUBLISHING

Animal Production Science, 2019, **59**, 1401–1427
https://doi.org/10.1071/AN18487

Perspectives on Animal Biosciences

Towards a new phenotype for tick resistance in beef and dairy cattle: a review

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Abstract. About 80% of the world's cattle are affected by ticks and tick-borne diseases, both of which cause significant production losses. Cattle host resistance to ticks is the most important factor affecting the economics of tick control, but it is largely neglected in tick-control programs due to technical difficulties and costs associated with identifying individual-animal variation in resistance. The present paper reviews the scientific literature to identify factors affecting resistance of cattle to ticks and the biological mechanisms of host tick resistance, to develop alternative phenotype(s) for tick resistance. If new cost-effective phenotype(s) can be developed and validated, then tick resistance of cattle could be genetically improved using genomic selection, and incorporated into breeding objectives to simultaneously improve cattle productive attributes and tick resistance. The phenotype(s) could also be used to improve tick control by using cattle management. On the basis of the present review, it is recommended that three possible phenotypes (haemolytic analysis; measures of skin hypersensitivity reactions; simplified artificial tick infestations) be further developed to determine their practical feasibility for consistently, cost-effectively and reliably measuring cattle tick resistance in thousands of individual animals in commercial and smallholder farmer herds in tropical and subtropical areas globally. During evaluation of these potential new phenotypes, additional measurements should be included to determine the possibility of developing a volatile-based resistance phenotype, to simultaneously improve cattle resistance to both ticks and biting flies. Because the current measurements of volatile chemistry do not satisfy the requirements of a simple, cost-effective phenotype for use in commercial cattle herds, consideration should also be given to inclusion of potentially simpler measures to enable indirect genetic selection for volatile-based resistance to ticks.

Additional keywords: blood parameters, host resistance, immune response, skin hypersensitivity, tick count, volatiles.

Received 7 August 2018, accepted 3 March 2019, published online 4 July 2019

Introduction

About 80% of the world's cattle are at risk of ticks and tick-borne diseases, both of which cause significant production losses. Economic losses from ticks and tick-borne diseases were estimated in 1996 to range from US$13.9 to US$18.7 billion per annum (de Castro 1997), with current estimates ranging from US$20 to US$30 billion per annum (Lew-Tabor and Rodriguez Valle 2016).

In a review of tick-control methods, Frisch (1999) suggested that cattle host resistance was the single most important factor affecting the economics of tick control. On the basis of recent reviews of the literature, host resistance is moderately to highly heritable (Burrow 2014; Burrow and Henshall 2014) and represents a low-cost, permanent solution requiring no extra labour or resources and incurring no additional costs to deliver beef and milk products (Frisch 1999). Acaricides or an anti-tick vaccine (developed in the 1990s, but subsequently withdrawn from the market in 2010) do not offer a permanent solution to tick control. Attempts to develop new anti-tick vaccines are ongoing (Guerrero *et al.* 2014; Lew-Tabor and Rodriguez Valle 2016), but new vaccines are highly unlikely to confer total protection against ticks. High host resistance is the key to effective long-term tick control, with total resistance being the ultimate aim (Frisch 1999). However, while improvements to acaricides and vaccines are continuously being pursued, improvements to the most important single factor controlling ticks, i.e. host resistance, is largely neglected (Frisch 1999).

The primary reason for such neglect is the difficulty and expense of identifying individual-animal variation in resistance to ticks. This constraint applies in research herds as well as in beef and dairy commercial and smallholder farms in both developed and developing countries. The purpose of the present paper is, therefore, to review information from the scientific literature to gain a better understanding of the factors affecting resistance of cattle to ticks as well as the biological mechanisms of host tick resistance, with the aim of identifying potential new phenotypes that can be evaluated in very large numbers of animals for tick resistance. The review will also briefly examine possibilities for the genetic improvement of tick resistance and incorporating economic weightings for tick resistance in breeding objectives aimed at simultaneously improving economically important productive and adaptive traits.

The need for a new phenotype for tick resistance

Cattle researchers have used single or repeated counts of the number of engorging ticks (i.e. ticks between 4.5 and 8 mm in diameter) on one or both sides of each animal following artificial or field infestation (Wharton and Utech 1970), so as to identify individual-animal variation in tick resistance. Tick counts are very time-consuming and require skilled animal technicians as well as expensive infrastructure to constrain animals simultaneously if reasonable numbers of animals are to be counted in a single day. The presence of ticks is also highly seasonal and, hence, animals need to be mustered at times when variation in tick numbers occurs across animals in a cohort group if valid tick counts are to be achieved using natural tick infestations. Alternately, artificial tick infestations can be used, but they require tick-breeding facilities and skilled laboratory technicians to deliver specific quantities of tick larvae for on-farm infestations. In regions where multiple tick species infest cattle, use of artificial infestations are also unlikely to be representative of tick loads under natural infestations.

In an attempt to simplify the tick-counting process, a system of single or repeated visual scores of the number of engorging ticks on one side of the animal following field infestations was implemented (Prayaga *et al*. 2009). Scores ranging from 0 (low) to 5 (high) were used. Tick scores do not require the same level of infrastructure as tick counts and, consequently, the rate of throughput of animals per day can be increased. However, the heritability of tick score is considerably lower than the heritability of tick count (Burrow 2014) and tick scores are subject to most of the other constraints that apply to tick counts. Hence, they are also very difficult to implement under research, commercial and smallholder production systems. A simpler, more cost-effective method of identifying individual animal variation in resistance to ticks (phenotyping) under research, commercial and smallholder production systems is urgently required to enable genetic and management improvements in host resistance to ticks.

Desirable features of a new tick-resistance phenotype

Desirable aspects of any new tick-resistance phenotype were foremost among considerations of this review. Those desirable features include the need for the new phenotype(s) to be

- moderately to highly heritable and strongly correlated with the current ‘gold standard’ tick-count phenotype, to enable ongoing application of previous research results based on tick counts, rather than having to repeat much of that previous research; to enable assessment of heritabilities and genetic correlations, large numbers of animals will need to be simultaneously recorded in well designed contemporary groups for both tick count and the new phenotype(s), and ideally also for other economically important traits where feasible;
- cost-effective for use in extensive pastoral production systems, and ideally without the need to muster animals on repeated occasions to derive the phenotype;
- capable of being reliably scheduled at a nominated point in time that suits management requirements, rather than at times when animals are known to have at least moderate levels of tick infestation, as is the current requirement;
- identifiable on the day of measurement, to enable management decisions while animals are still in hand (e.g. to draft off susceptible animals for ongoing closer management and culling from the breeding herd); and
- able to accommodate non-linear relationships (e.g. threshold responses that might trigger differential management decisions).

Applying potential new phenotype(s) through genomic selection

Recent reviews of the literature indicate that resistance of beef and dairy cattle to ticks is moderately to highly heritable, providing good opportunities to directly improve resistance of cattle to ticks through crossbreeding and within-breed selection (Burrow 2014; Burrow and Henshall 2014). On the basis of several independent studies in tropically adapted cattle in northern Australia, it was also concluded that selection to improve resistance to any one stressor of tropical environments will improve resistance to other stressors. That conclusion was particularly true for resistance to ticks, worms and heat stress, where genetic correlations were consistently moderately positive, suggesting that the same or closely linked genes affect all three traits (Burrow 2012).

The existence of favourable genetic correlations among adaptive traits does not extend to genetic correlations between adaptive and productive traits. Except for heat stress measured by rectal temperatures under conditions of high ambient temperatures, resistance to most environmental stressors appears to be largely genetically independent of productive traits such as growth, reproduction and product quality, albeit the conclusions are based on only a small number of Australian studies (Burrow 2014). It can, therefore, be concluded that, in cattle well adapted to tropical and subtropical environments, there are no major strongly antagonistic correlations among the traits that would preclude simultaneous genetic improvement in all the traits in tropical cattle-breeding objectives.

Gibson and Bishop (2005) suggested that adaptive traits are ideal candidate traits for use of genomic information due to the difficulty and expense of collecting the essential phenotypes needed for conventional phenotype-based selection. Those authors predicted that the use of genomic information based on single-nucleotide polymorphisms (SNPs) or quantitative trait loci would be most beneficial for traits of low heritability or traits that are difficult, expensive or impossible to record routinely. They also suggested that the use of genetic markers could be particularly beneficial in the low- to medium-input systems of the developing world, where disease resistance and adaptation of livestock are critically important for the sustainable livelihoods of poor farmers. Although their predictions about usage remain valid, it has since become clear that it is very unlikely that any individual SNP will account for a significant proportion of the genetic variation for economically important traits, as was hypothesised at that time. Rather, genetic variation for most traits of economic importance is underpinned by a large number of mutations, each of small effect (MacLeod *et al.* 2016).

Resistance of cattle to ticks appears to follow this genetic architecture, i.e. genome-wide association studies (see e.g. Gasparin *et al.* 2007; Machado *et al.* 2010; Porto-Neto *et al.* 2010, 2011*a*, 2011*b*, 2012, 2014; Turner *et al.* 2010; Cardoso *et al.* 2015; Mota *et al.* 2016; Mapholi *et al.* 2016) have identified few, if any, associations of large effect.

Given this trait architecture, genomic selection (Meuwissen *et al.* 2001, 2016) is likely to be a more effective way of improving tick resistance. Genomic selection uses a large reference population of animals genotyped with genome-wide SNP markers, and phenotyped for the trait of interest, to derive the effect of each SNP (reflecting the effect of the causal mutations affecting the trait captured through linkage disequilibrium with the SNP). However, it has not been possible to develop genomic-prediction equations for resistance of cattle to ticks, largely due to the ongoing inability to cost-effectively identify individual-animal variation in resistance.

To achieve the levels of accuracy required for traits such as cattle resistance to ticks, given the moderate heritabilities of the trait, very large cattle resource populations that have been accurately recorded for the trait are needed (Goddard and Hayes 2009). Such populations are already being established in several countries where ticks are endemic. If a cost-effective measure of tick resistance can be developed and validated, those resource populations would readily include the new tick-resistance phenotype in their recording programs.

Incorporating tick resistance as a trait in breeding objectives

Once a practical and cost-effective tick phenotype is available for on-farm use and sufficiently large reference populations are developed, tick resistance could be incorporated into the breeding objectives of cattle genetic-improvement programs. In most cases, it could be expected that tick resistance will be an additional economic trait for consideration in already complex breeding objectives (Reis *et al.* 2017). Since tick counts are, in general, weakly correlated with other economic traits in cattle (Burrow 2001; Biegelmeyer *et al.* 2017), the emphasis to be given in a selection index to the tick-related criterion will be critical to determine the genetic progress that can be achieved for tick resistance.

Deriving economic values for tick resistance simultaneously with other adaptive and productive traits is the most appropriate way to incorporate this new trait in cattle-selection programs (e.g. Amer *et al.* 2001). Nonetheless, bio-economic modelling of tick parasitism and epidemiology for specific cattle-production systems and environments is challenging and scarce in the recent livestock literature (Grisi *et al.* 2014; Mapholi *et al.* 2014). Recent work from Brazil, using a stochastic model to account for death risk and reduced productivity, has demonstrated a low importance for tick counts in a global breeding objective, with values of 12.9% for Brangus (Simoes 2017) and 3.8% for Hereford and Braford cattle (Costa *et al.* 2018). However, these values were derived under production systems in subtropical environments where ticks (and, therefore, tick-borne diseases) were controlled without major difficulties by chemical treatments and appropriate management. Therefore, additional research is required to evaluate the economic values of tick resistance under more challenging environments, with larger tick loads and widespread resistance of ticks to chemicals, particularly in taurine herds raised under tropical conditions or where cattle are managed in production systems where ticks cannot be controlled by management options due to expense or logistical difficulties. In systems where ticks cannot be controlled, then economic values and the relative importance of tick resistance in breeding objectives will certainly be much higher.

Reis *et al.* (2017) proposed different scenarios to include tick resistance as an extra breeding goal for Brazilian Hereford and Braford cattle. They concluded that availability of highly accurate genomic information from multi-trait calibration sets would be desirable to achieve faster genetic progress for complex breeding goals. Moreover, due to the low correlation with other economically important productive traits, they suggested that if the goal is to breed specific lines of tick-resistant cattle, assigning a relative importance of 50% for counts in the selection index would be a suitable alternative. This would assure the necessary genetic progress for resistance to ticks (more than 0.5 genetic s.d. per generation) in the target population, while retaining the necessary balance to ensure genetic progress in other economically relevant traits. This could become a strategy to create market differentiation and advantage for taurine cattle breeds or composites selected under tropical and subtropical conditions. Genomic selection could accelerate development of such specialised lines. However, such a high weight on tick resistance would greatly compromise genetic gain for other traits

such as meat quality. An alternative use of the genomic information would be to develop new composite breeds that stack tick-resistance chromosome segments together with meat quality- and reproduction-improving segments, so as to maximise performance of the resulting animals.

Tick species that infest cattle

Ticks are small to medium-sized blood-sucking arachnids, with ~900 tick species occurring worldwide, although most have a regional distribution (Guglielmone *et al.* 2010). Tick species affecting cattle are 'hard ticks' (Ixodids, see for example Horak *et al.* 2009) and are found in tropical and subtropical regions of the world. They vary across regions, but include subspecies of *Rhipicephalus* (previously known as *Boophilus*), *Amblyomma* and *Hyalomma*. Cattle in Asia, Australia and Central and South America are affected by members of the Asian tick *Rhipicephalus microplus* complex, whereas cattle across Africa are affected by species from all three genera. Infestation of cattle by these species has a direct impact on production, such as, for example, growth and milk production, efficiency of feed utilisation, reproductive performance (Seebeck *et al.* 1971; O'Kelly and Kennedy 1981; O'Kelly *et al.* 1988) as well as affecting indirectly through transmission of tick-borne diseases (Lehmann 1993). Additional hide and udder damage resulting from tick bites reduces or negates the sale of cattle hides and reduces milking ability in the affected cattle.

Of major concern across Africa is the recent partial or complete displacement of some indigenous tick species with the more aggressive Asian tick (*R. microplus*), which was introduced with the importation of cattle to Africa, and which has proven to be a very efficient vector of tick-borne diseases, particularly of *Babesia bovis*. Displacement of species has been reported from Ivory Coast and Cameroon (Madder *et al.* 2011; Mamoudou *et al.* 2016; Boka *et al.* 2017), South and southern Africa (Tønnesen *et al.* 2004; Nyangiwe *et al.* 2011, 2013) and Tanzania and eastern Africa more generally (Lynen *et al.* 2008; Horak *et al.* 2009). In addition to the displacement of some tick species, the Tanzanian data, in particular, indicate that the advance of *R. microplus* and the retreat of *R. decoloratus* are associated with the 58-mm isohyet and the 22–23°C isotherm and suggest a higher-temperature tolerance for *R. microplus* (Lynen *et al.* 2008). Those authors anticipated that climate change is likely to increase the spread of *R. microplus*, and, consequently, *Babesia bovis*, into new areas of Africa.

In Australia, the Australian cattle tick, *Rhipicephalus australis*, formerly known as *R. microplus*, has been determined to be a distinct species and can be distinguished from *R. microplus* on the basis of morphological, genetic and mating criteria (Labruna *et al.* 2009; Estrada-Peña *et al.* 2012). The *R. microplus* complex now consists of at least three genotypes or species (Clades A–C) based on molecular systematics, named *R. microplus*, including *Rhipicephalus annulatus* and *R. australis* (Burger *et al.* 2014; Low *et al.* 2015; Roy *et al.* 2018). It is not yet known how their biological differences may affect the selection of tick resistance in cattle, but any genetic-improvement program will need to consider this.

As indicated above, the tick of major concern for cattle in regions excluding Africa is *R. microplus*. However, several other ticks in these regions also affect cattle. In the United States, the main tick species of concern to cattle include *Amblyomma americanum*, which causes hide damage 'tick worry' (Barnard *et al.* 1992), while *Amblyomma maculatum* causes a condition known as 'gotch ear' (Edwards 2011) and has a potential role in the spread of heartwater. Both species occur in the south-eastern states (Sonenshine 2018; Raghavan *et al.* 2019). *Dermacentor andersoni* (western Canada and United States) can cause tick paralysis in cattle (James *et al.* 2006; Lysyk *et al.* 2009). Recently, *Haemaphysalis longicornis*, the vector for the virulent Ikeda strain of *Theileria buffeli*/*orientalis*, has been introduced into the United States, but has not yet been established endemically (Beard *et al.* 2018). Both *Rhipicephalus annulatus* and *R. microplus* remain serious problems in Mexico as well as southern Texas (Lohmeyer *et al.* 2011). *Rhipicephalus annulatus* occurs endemically in the Mediterranean, and middle-eastern, central, northern and West Africa (Walker *et al.* 2003). Both tick species can transmit *Anaplasma marginale* (the causative agent for bovine anaplasmosis), *B. bovis* (the causative agent for Asiatic red water) and *Babesia bigemina* (the causative agent for African red water; Walker *et al.* 2003). In Central and South America, in addition to *R. microplus*, *Amblyomma sculptum*, *A. tonelliae* and *A. triste* are the main ticks that affect cattle (Nava 2017). However, given recent changes in the taxonomic status of various *Amblyomma* species in the Neotropics, their geographic distributions need to be reassessed (Nava *et al.* 2014; Lado *et al.* 2018). For example, it has been proposed that *A. maculatum* and *A. triste* should be synonymised (Lado *et al.* 2018), while *A. sculptum* and *A. tonelliae* have only recently been reinstated or described as new species (Nava *et al.* 2014). Their economic importance lies in the damage to hides and general impact on host productivity.

In Australia and New Zealand, the introduction of *H. longicornis* from Asia has introduced pathogenic genotypes of *Theileria buffeli*/*orientalis*, notably Ikeda (Izzo *et al.* 2010; Kamau *et al.* 2011; McFadden *et al.* 2011). This introduction has been responsible for oriental theileriosis outbreaks along the eastern coast of Australia and the North Island of New Zealand and has recently spread to the South Island as well (Kamau *et al.* 2011; McFadden *et al.* 2011, 2016). Ticks that are endemic to Australia and are vectors of the more benign genotypes of *T. buffeli*/*orientalis* (e.g. buffeli, chitose and Type C) include *Haemaphysalis bancrofti* and *Haemaphysalis humerosa* (Barker and Walker 2014). In Asia, *H. longicornis* is the main vector of the Ikeda strain of *T. buffeli*/*orientalis* and occurs in Japan, Korea, and parts of China and Russia (Barker and Walker 2014). The Ikeda strain has been imported into Pakistan and Vietnam from Australia, but it remains to be seen whether an appropriate tick vector is present (Gebrekidan *et al.* 2017*a*, 2017*b*).

In Africa, in addition to *R. microplus*, a large number of tick species are of economic and veterinary importance for cattle. Members of the genus *Amblyomma* mainly transmit *Ehrlichia ruminantium*, the causative agent of heartwater and include *A. hebraeum* (Botswana, southern Mozambique, South Africa, southern Zimbabwe, Swaziland), *A. lepidum* (central and eastern

Sudan, Ethiopia, southern Somalia, eastern Uganda, Kenya and the northern region of central Tanzania), *A. pomposum* (Angola, western Zambia and southern Democratic Republic of Congo) and *A. variegatum* (central, eastern, southern Africa extralimital to South Africa and West Africa; Walker and Olwage 1987; Walker *et al.* 2003). These species also transmit *Theileria mutans* and *T. velifera*, causative agents of benign bovine theileriosis, while *A. variegatum* is a vector of *Ehrlichia bovis* that causes bovine ehrlichiosis. *Haemaphysalis punctata* transmits *Theileria buffeli*, the cause of bovine theileriosis and occurs mainly in Europe, the northern Mediterranean, eastward into central Asia, but also extends into northern Africa (Walker *et al.* 2003). *Hyalomma anatolicum* transmits *Theileria annulata* as well as *Trypanosoma theileri*, the causative agents for tropical theileriosis and benign bovine trypanosomiasis in cattle respectively. It is widespread from northern Africa, the Mediterranean, the Middle East, India, Iran, China and southern Russia. *Hyalomma scupense* (=*H. detritum*) vectors *Theileria annulata* and occurs in the Mediterranean parts of northern Africa as well as northern-central Sudan. *Hyalomma rufipes* is the vector for *Anaplasma marginale* and occurs in most parts of Africa and extends into southern Europe and eastward to central Asia. *Hyalomma lusitanicum* also vectors *T. annulata* and is found in Mediterranean regions of Algeria and Morocco. *Hyalomma truncatum* occurs in Africa south of the Sahara and causes toxicoses known as sweating sickness in cattle (Walker *et al.* 2003). *Rhipicephalus annulatus* occurs in central, northern and West Africa and south-eastern Sudan. *Rhipicephalus* (*Boophilus*) *decoloratus* transmits *Babesia bigemina*, *Anaplasma marginale* and *Borrelia theileri*, the cause of spirochaetosis in cattle. It occurs in most regions south of the Sahara (Walker *et al.* 2003). *Rhipicephalus appendiculatus* and *R. zambeziensis* are the vectors for *Theileria parva*, the causative agent for Corridor disease, East Coast fever and Zimbabwean theileriosis (January disease), occurring from southern to central Africa (Walker *et al.* 2000). East Coast fever is considered to have the largest economic impact on cattle in Africa, with an estimated 1 000 000 deaths per annum (Nene *et al.* 2016). Corridor disease is found wherever African buffalo (*Syncerus caffer*), *R. appendiculatus*, and cattle co-occur. The only exception to this is in South Africa where large Corridor disease-free African buffalo herds are kept within the endemic region for *R. appendiculatus*, due to strict disease and movement management by the Department of Agriculture, Forestry and Fisheries of South Africa (Pienaar *et al.* 2011; Laubscher and Hoffman 2012).

Figure 1*a* shows the worldwide distribution of the economically important members of the *Boophilus* subgenus, indicating the endemic nature of the tick problem globally. Additional distributions for the major economic ticks are also provided in Fig. 1*b–d*. Given the large number of tick species that can transmit the same pathogens, selection for tick resistance across species boundaries should be an important consideration to prevent replacement of one tick species with another.

Factors affecting cattle tick resistance

Breed effects

Cattle evolved into two distinct geographic groupings ~610 000–850 000 years ago (MacHugh *et al.* 1997). *Bos taurus* breeds are adapted mostly to temperate environments in Europe and the Near East, and include British and European breeds most suited for milk (e.g. Holstein–Friesian, Jersey) or beef (e.g. Angus, Hereford, Charolais) production. Zebu or *Bos indicus* breeds evolved in more tropical environments in southern Asia (MacHugh *et al.* 1997) and include breeds that have evolved for specialist milk (e.g. Sahiwal, Red Sindhi) and beef (e.g. Brahman, Nellore) production. A third distinct grouping evolved more recently in tropical environments, and those breeds are now commonly referred to as tropically adapted taurine breeds. These are true *Bos taurus* (Frisch *et al.* 1997; Hanotte *et al.* 2003; Gibbs *et al.* 2009) that retain some of the productive attributes of *Bos taurus*, but they are better adapted to tropical environments than is European *Bos taurus*. They include the southern African Sanga breeds (e.g. Afrikaner, N'guni, Tuli), West African humpless breeds (e.g. N'dama), and Criollo breeds of Latin America and the Caribbean (e.g. Romosinuano). Historical reports describing these breeds suggested that they were admixtures of *Bos indicus* and *Bos taurus.* However, on the basis of recently available molecular-genetic tools, it is now widely accepted these breeds are true *Bos taurus*, although some degree of admixture of the breed types may have occurred over recent decades.

Numerous historical and more recent studies have indicated that large differences exist between beef- and dairy-cattle breeds in resistance to a wide range of tropical environmental stressors and factors that affect animal performance, including resistance to ticks. As indicated by Hewetson (1972), it has long been recognised that some breeds of cattle are more resistant to infestations with ticks than are others (e.g. Lush 1927; Zawadowsky 1931; Kelley 1932; Bonsma 1940; as cited by Hewetson 1972). These and more recent reports (e.g. Seifert 1971; Hewetson 1972; Utech *et al.* 1978; Frisch 1981, 1987; Utech and Wharton 1982; Madalena *et al.* 1985, 1990; Sahibi *et al.* 1997; Frisch and O'Neill 1998; Mwangi *et al.* 1998; Wambura *et al.* 1998; Frisch *et al.* 2000; Berman 2011; Ibelli *et al.* 2012) from Australia, Brazil and Africa have indicated that *Bos indicus* breeds have a greater resistance to ticks than do European *Bos taurus* breeds, with the tropically adapted taurine breeds being more resistant than European breeds, but not as resistant as *Bos indicus* (e.g. Spickett *et al.* 1989; Scholtz *et al.* 1991; Latif 2006; Muchenje *et al.* 2008).

These and many other studies have shown that, in temperate environments, there are substantial differences in growth, milking ability, reproduction and product quality among these different cattle breeds. However, in cattle grazed at pasture in tropical environments, the differences in performance are generally masked by the effects of environmental stressors on those productive attributes. This led to recommendations that, for most purposes in the tropics, comparisons of performance should be made across general breed types or groupings (*Bos taurus*, British and European; *Bos indicus*; and tropically adapted taurine) rather than across specific breeds (Burrow *et al.* 2001). These results also allowed development of a table of comparative rankings of the different breed types for different productive and adaptive attributes in both temperate and tropical environments (see Burrow 2012). It was concluded that any breeding program designed for cattle grazed at pasture in tropical environments must consider the impacts of both productive and

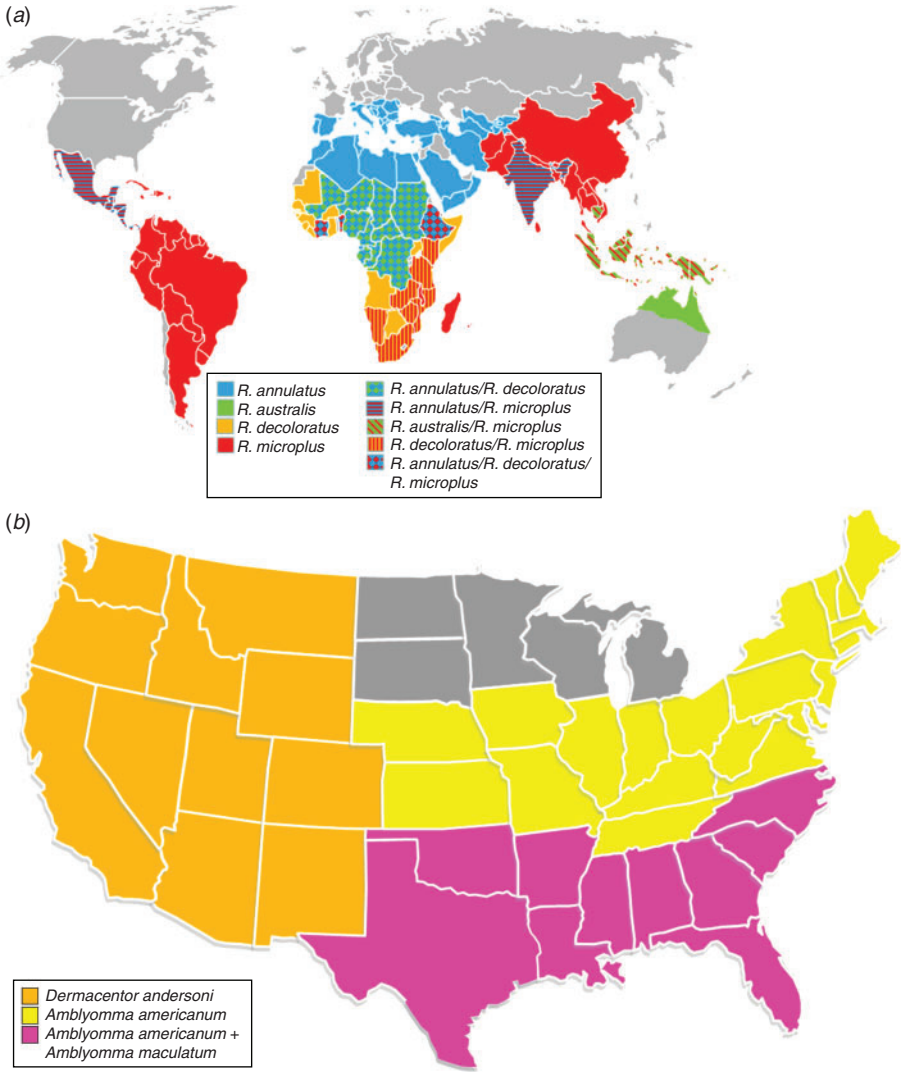

Fig. 1. (*a*) Worldwide distribution of the most economically important members of the *Boophilus* subgenus. Adapted from Burger *et al*. (2014). Most other tick species of economic importance also fall within this larger distribution, except as discussed in the text. Distribution maps for these exceptions are shown in (*b*)–(*d*). The presence of ticks in a country does not imply distribution throughout the country, with presence being dependent on specific biomes. Grey regions indicate an absence of species. (*b*) Ticks of economic importance to cattle in the United States of America (excluding the subgenus *Boophilus*). Orange indicates the distribution of *Dermacentor andersoni*, yellow the distribution of *Amblyomma americanum* and pink the distribution of *Amblyomma americanum* and *A. maculatum*. The presence of ticks in a state does not imply distribution throughout the state, but depends on the presence of specific biomes and habitat restrictions. Data were collated from James *et al.* (2006), Sonenshine (2018) and Raghavan *et al.* (2019). Grey regions indicate an absence of tick species. (*c*) Major ticks of economic importance to cattle in Africa (excluding the subgenus *Boophilus*). Distributions are indicated for *Amblyomma* (left panel), *Hyalomma* (central panel) and *Rhipicephalus* (right panel). The presence of ticks in a country does not imply distribution throughout the country, but depends on the presence of specific biomes and habitat restrictions. Data were collated from Walker and Olwage (1987) and Walker *et al.* (2000, 2003). Grey regions indicate an absence of tick species. (*d*) Major ticks of economic importance to cattle in the Palearctic and Australasian regions. The presence of ticks in a country does not imply distribution throughout the country, but depends on the presence of specific biomes and habitat restrictions. Data were collated from Estrada-Peña *et al*. (2013) and Barker and Walker (2014). Grey regions indicate an absence of tick species.

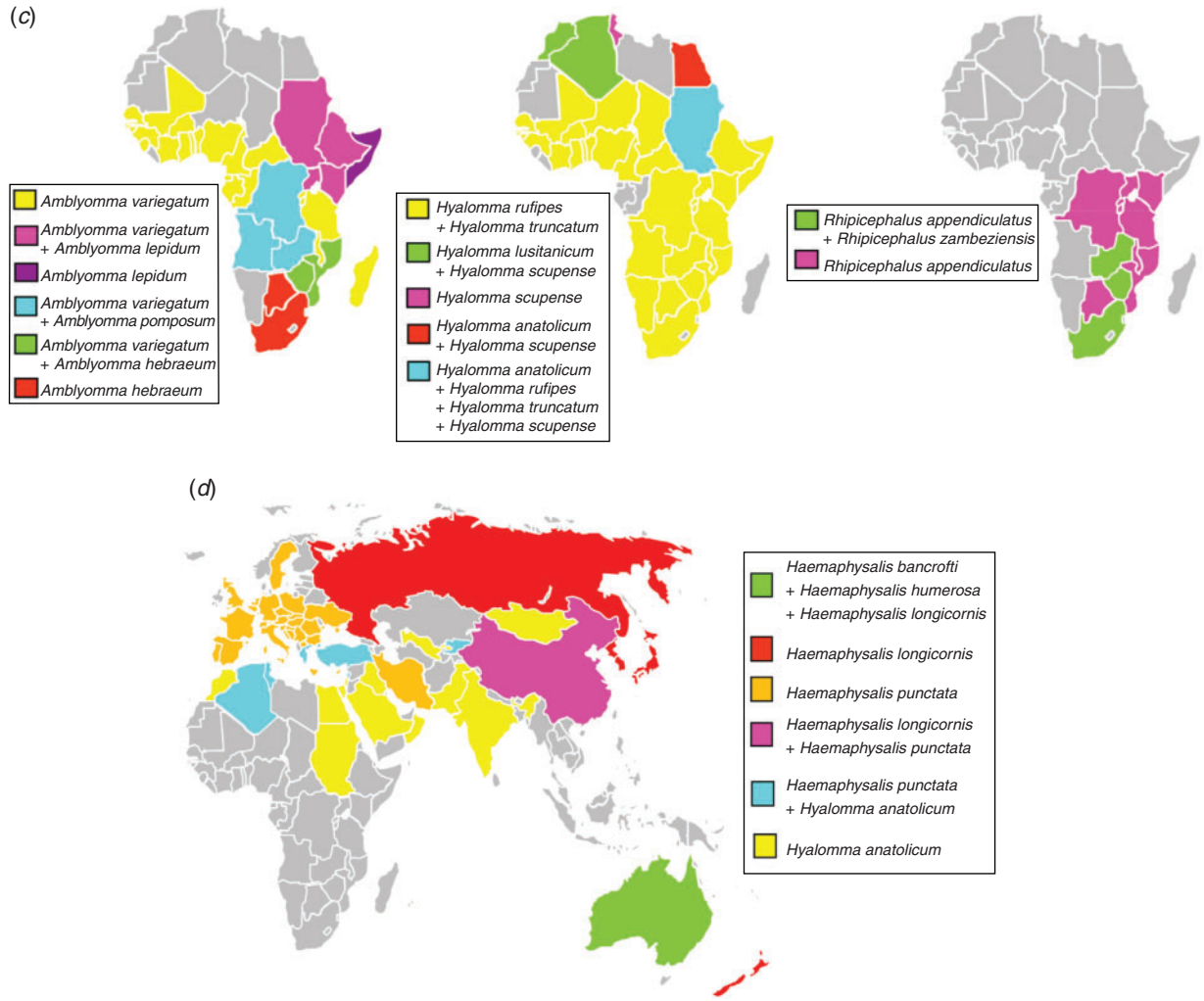

Fig. 1. (*Continued*)

adaptive attributes, even though adaptive traits (and some productive traits) are generally very difficult and expensive to measure (Burrow 2012).

Other effects

There are several additional animal and environmental factors that affect resistance of cattle to ticks, and, hence, must be considered in the design of cattle-resource population(s) established to measure cattle tick resistance. Table 1 briefly summarises those factors.

Cattle resistance to ticks

Innate or acquired resistance and is it the same in different breeds?

It is important to understand whether resistance of cattle to ticks is innate or acquired resistance. If it is an acquired resistance, then the timing of any assessment of an animal's resistance will be critically important (i.e. it should occur only after all animals have experienced repeated exposures to ticks, so that the assessment is undertaken after the animals have acquired their resistance).

Legg (1930) was the first person known to report that aspects of tick resistance indicated that all cattle show considerable resistance to ticks in the sense that only a relatively small percentage of larval ticks ever reach maturity. However, most studies have indicated that all animals are susceptible to tick infestations at their first challenge and, subsequently, develop different degrees of resistance. Later studies (e.g. Hewetson 1972; Sutherst 1983*a*) have indicated that resistance of cattle to ticks is acquired rather than innate, with all cattle being susceptible at their first (and early) exposures to ticks. Hewetson (1972) showed that *Bos indicus* Sahiwal cattle were as susceptible to ticks as were crossbred Sahiwal × Jersey cattle at the time of their first infestation, but, over the following three infestations, the Sahiwals became more resistant. This was reflected in heritability estimates, with the heritability of tick resistance being zero at the first three infestations, and the estimates increasing to 0.28 and 0.42 at the fourth and fifth infestations respectively.

The only study known to suggest that cattle tick resistance could be an innate resistance is that of Riek (1962). In that study, the resistance of *Bos taurus* and *Bos indicus* and of their

Table 1. Animal and environmental factors affecting resistance of cattle to ticks (excluding breed)

Parameter	Impact on cattle tick resistance	Source
	Animal factor	
Sex	Male calves are more susceptible to ticks than contemporary female calves	Utech and Wharton 1982; Burrow *et al.* 1991
Age	In calves up to 8 months of age, older calves from the same crop are more resistant than the younger calves, reflecting time needed for animals to acquire their resistance to ticks	Utech and Wharton 1982
Differences in resistance between F_1 and F_2 and subsequent generation crosses of *B. indicus* × *B. taurus*	Little genetic variance is evident for tick resistance in F_1 generations of Zebu × British crosses, but considerable genetic variation exists in F_2 and F_3 generations, attributable to dominance or different frequencies of additive genes	Seifert 1971; Frisch 1981, 1987
Pregnancy status	There is an inconsistent effect of pregnancy on reliability of tick counts	Wharton and Utech 1970
Lactation status	In dairy cattle and dairy × Brahman cattle, tick resistance of cows is lowered by lactation and during the third trimester of pregnancy; lactation also reduces the reliability of tick counts; and the peripartum period has a significant effect (calving and post-calving) on tick infestation; average tick counts are significantly higher in first-lactation animals followed by those at second, third and fourth or subsequent lactations	Wharton and Utech 1970; Utech and Wharton 1982; da Silva *et al.* 2014
Skin thickness and gland concentration	There is no correlation between skin thickness or sweat gland or sebaceous gland concentrations and the degree of resistance by cattle to ticks	Riek 1962
Coat type (very sleek to very woolly)	There are favourable correlations between total tick count and coat thickness and weight of hair samples in Senepol × Nellore cattle but not in Angus × Nellore (note: the paper did not specify generation of cross; so. if these are F_1 crosses. the result is more plausible than if they were F_2 or subsequent generations); relationships between tick counts and coat score are positive and linear in Nguni and quadratic in Bonsmara heifers	Ibelli *et al.* 2012; Marufu *et al.* 2013
Ability of animal to self-groom or be groomed (e.g. licking rubbing)	Licking and other forms of host behaviour reduce the number of female ticks that survive to fall as engorged adults from the host	Snowball 1956
	Environmental factor	
Time of year (season)	Differences in resistance are more readily recognised in summer than in winter, and when tick infestations are reasonably heavy	Seifert 1971; Sutherst 1983*b*; Sutherst *et al.* 1983*a*, 1983*b*, 1988; Bekele 2002; Gasparin *et al.* 2007; Machado *et al.* 2010; Mapholi *et al.* 2016
Presence of other ecto- and endo-parasites	Animals that are treated to control other ecto- and endo-parasites carry fewer ticks than animals which are not treated	Turner and Short 1972; Turner 1982; Frisch and Vercoe 1982, 1984; Frisch and O'Neill 1998
Presence of other stressors, e.g. high temperatures and humidity, nutritional stress	Reliability of tick counts is affected by these stressors	O'Kelly and Seifert 1969, 1970; Wharton and Utech 1970; Turner and Short 1972; Turner 1982; Sutherst 1983*b*; Sutherst *et al.* 1983*a*, 1983*b*, 1988
Tick-count observer	High error noted in tick counts undertaken by novice observers, with a strong message that selection for tick resistance is not easy for inexperienced observers or those temperamentally ill-suited to meticulous counting to attain reliable tick counts	Seifert 1971

crosses to tick infestation was assessed by repeated experimental infestation. Two types of resistance were observed, namely, an acquired resistance that became evident after repeated exposure and an innate resistance that was present in some animals, never previously exposed, on their first infestation (Riek 1962). Acquired resistance was least apparent in purebred *Bos taurus*, but considerable variation in the degree of resistance was observed among individuals within the respective breed groups. Innate resistance was observed in some *Bos indicus*. The mechanism appeared to persist in subsequent exposures, but its significance was difficult to assess (Riek 1962).

On the basis of these findings, it should be assumed that cattle tick resistance is acquired for all cattle-breed types (beef and dairy cattle and across *Bos taurus* and *Bos indicus* breeds), with allowance needing to be made for animals to acquire resistance before assessments of tick resistance are undertaken. On the basis of practical research experience, cattle that are reared on pasture in tick-endemic areas can be assumed to have acquired their

resistance to ticks by the time they are weaned at 6–9 months of age. In production systems where weaning is routinely practiced, weaning tends to occur around the start of the tropical 'dry season', to ensure that cows are not lactating during periods of nutritional stress. The start of the 'dry season' also tends to coincide with the start of cooler months when tick infestations are lower and less reliable, on the basis of studies summarised in Table 1. Hence, it is recommended that assessments of cattle tick resistance be undertaken from the commencement of warmer periods in post-weaning cattle (e.g. in the southern hemisphere that would equate to calf weaning from May to July and tick-resistance assessments undertaken from August or September, when the calves are 9–12 months of age).

Is cattle tick resistance the same for different tick species?

An additional question that needs consideration is whether cattle tick resistance is similar for the different tick species. Only the studies of Wagland *et al*. (1985), de Castro *et al*. (1989) and Miranpuri (1989) are known to have examined this question.

Wagland *et al*. (1985) exposed cattle simultaneously to both *Haemaphysalis longicornis* (bush tick) and *Boophilus microplus* (cattle tick). Cattle that had never been exposed to either tick species were equally susceptible to both species. Cattle with acquired resistance to both species ranked consistently for levels of resistance to each species when infested separately. Concurrent infestation with *H. longicornis* had no effect on ranking for resistance to *B. microplus.* The coefficient of concordance between the rankings of individuals on their levels of resistance to both species of tick was positive but not statistically significant. The authors concluded the tick antigens stimulating host resistance were species-specific and, therefore, did not provide cross-protection, an important consideration in the development of anti-tick vaccines. However, the favourable correlation in rankings of individual animals for resistance to the two species suggested that co-selection for resistance to different tick species was achievable (Wagland *et al*. 1985).

de Castro *et al*. (1989) co-infested *R. appendiculatus*-resistant cattle with *R. appendiculatus* and *R. pulchellus*, limiting each tick species to an ear. Intense pruritis, grooming and acute inflammation were observed in the ears infested with *R. appendiculatus*, but no reaction was observed in the opposite ears infested with *R. pulchellus*. More *R. pulchellus* than *R. appendiculatus* nymphs were obtained from resistant animals, although more nymphs of both species were obtained from susceptible cattle than from resistant cattle. However, the mean engorged weights of *R. pulchellus* nymphs obtained from resistant and susceptible cattle were not significantly different. The authors concluded that different antigens may be involved in development of resistance to these tick species.

Miranpuri (1989) investigated the effect of repeated pure infestations with *Boophilus microplus* on susceptibility to subsequent pure infestations with *Hyalomma anatolicum*, and the effects of infestations with both tick species on susceptibility to a series of mixed infestations. Results showed that cattle acquired resistance to both tick species after repeated pure infestations, but animals with acquired resistance were as susceptible to the other tick species as were animals that had never been exposed to ticks of either species. After repeated pure infestations with both tick species, cattle responded to five mixed infestations, showing a high degree of resistance to *B. microplus* and low resistance to *H. a. anatolicum* (mean yield for *B. microplus* was 10 $\pm$ 8.1 ticks per host after the first mixed exposure and declined to 1.3 $\pm$ 1.7 after the fifth, whereas the mean yield for *H. a. anatolicum* was 71.4 $\pm$ 11.3 ticks per host following the first exposure and declined to 37.3 $\pm$ 7.8 after the fifth). The author concluded that host responses elicited to one species did not provide cross-resistance to the second species used in that study.

On the basis of these studies, it is clear that further studies are needed to determine whether co-selection for resistance to different tick species is feasible. Hence, any studies aimed at development of a more cost-effective phenotype for cattle tick resistance should be undertaken in a region where cattle are infested by multiple tick species. In addition, assessments of host tick resistance should take account of the number of ticks of each species infesting individual animals.

Biological mechanisms of cattle tick resistance

Clinical signs of cattle tick resistance

Resistance of cattle to ticks depends on the animal's capacity to acquire immunity in response to tick exposure, but how the immunological mechanism affects tick development and mortality is not well defined. Johnston and Bancroft (1918, cited by Hewetson 1972) suggested the following criteria to assess resistance of cattle to ticks:

(1) ticks failing to complete their life-cycles;
(2) cattle that have light tick infestations relative to other animals that are heavily infested;
(3) female ticks failing to engorge in numbers similar to those on susceptible animals under the same conditions; and
(4) engorged ticks failing to lay a normal number of eggs or to lay eggs with a normal fertility.

Hewetson (1972) added the following two additional criteria:

(5) an increase in the time taken for female ticks to complete their parasitic life cycles; and
(6) a decrease in the mean weight of replete female ticks.

Other clinical signs of tick resistance that could be useful in defining a new phenotype include:

- anaemia affecting productive and reproductive traits (Lehmann 1993), with the removal of blood by the ticks (0.3 mL/tick; Seifert *et al.* 1968) accounting for depletion of some blood constituents (e.g. albumin, haemoglobin and cholesterol);
- depressed appetite and reduced dietary-nitrogen utilisation, reducing growth rates, milk production and reproductive performance (Seebeck *et al.* 1971; O'Kelly and Kennedy 1981; O'Kelly *et al.* 1988); and
- transmission of diseases through tick saliva, which in turn suppresses immune function and results in cattle mortality and morbidity (Lehmann 1993).

Of these, Criterion 2 is the basis of the current 'gold standard' for assessing cattle tick resistance. The remaining criteria have until now been regarded as being either too difficult to measure or too poorly correlated with tick counts to warrant consideration as a phenotype for tick resistance. However, as discussed further later in this

review, new protocols for assessing anaemia could contribute to a new and cost-effective tick-resistance phenotype.

Immunological mechanisms

Early studies from Belmont Research Station in north-eastern Australia on the mechanisms of acquired tick resistance in cattle have provided a large number of indicators of immunological causes. Tick-susceptible animals have decreased protein and dry-matter digestibility and increased nitrogen loss in urine. Infestation also depresses blood concentrations of albumin, haemoglobin, cholesterol and the enzymes alkaline phosphatase, lactate dehydrogenase and amylase (O'Kelly and Seifert 1969, 1970; O'Kelly *et al.* 1971). Other changes suggesting the immune system is implicated include increases in serum globulin, lymphocytes and eosinophils and a decrease in neutrophils (O'Kelly *et al.* 1971). Tick infestation also causes loss of proteins, which is not entirely explained by blood loss (Springell *et al.* 1971). The failure of the host to replenish depleted albumin and haemoglobin suggests a probable effect of tick toxin on protein metabolism. In addition, amylase type was moderately associated with tick resistance (Ashton *et al.* 1968). A further finding is that tick resistance is also correlated with lipid constituents of blood (O'Kelly 1968).

Subsequently, Wikel (1996, p. 1) undertook a detailed review of host immunity to ticks and developed the following conclusive summary:

> '. . . the tick–host–pathogen interface is characterised by complex immunological interactions. Tick feeding induces host immune regulatory and effector pathways involving antibodies, complement, antigen-presenting cells, T-lymphocytes and other bioactive molecules. Acquired resistance impairs tick engorgement, ova production and viability. Tick countermeasures to host defences reduce T-lymphocyte proliferation, elaboration of the T_H1 cytokines interleukein-1 and interferon-γ, production of macrophage cytokines interleukin-1 and tumour necrosis factor and antibody responses. The dynamic balance between acquired resistance and tick modulation of host immunity affects engorgement and pathogen transmission.'

With this wide array of effects, it is understandable why development of a simple, cost-effective phenotype for tick resistance still remains to be achieved.

However, many researchers have since investigated different aspects of the immunological function associated with cattle tick resistance, using different approaches as summarised briefly below. Their results have provided greater insight into specific aspects of immune competence, which might be targeted when developing a new phenotype for cattle tick resistance.

Stear *et al.* (1989) assessed two consecutive crops of 75% Brahman × 25% Shorthorn calves for resistance to *Boophilus microplus* in Australia in May, July and October 1983. Although the level of resistance to artificial tick infestation varied considerably among seasons, the animals maintained very similar rankings for resistance in all three seasons. The cattle were typed for 30 bovine Class-1 lymphocyte antigens, with antigens W6 and CA31 found to be associated with susceptibility to tick infestation. However, none of the other lymphocyte antigens showed strong associations with either resistance or susceptibility. The authors believed that W6 was unlikely to be useful as an indicator of susceptibility on its own because there could be other unidentified factors that play a role in determining whether or not W6 exerts a significant effect on tick resistance. The other significant antigen, CA31, is a subgroup of W6, i.e. all cattle with CA31 also possess W6. Hence, the association of W6 with tick susceptibility may be due to the presence of CA31 in some W6-positive cattle.

In a follow-up study, Stear *et al.* (1990) used natural infestations of the cattle tick and levels of buffalo fly and faecal-nematode egg concentrations to assess resistance in tropically adapted male and female taurine animals in the post-weaning period, when the animals were between 9 and 19 months of age. In addition, the male animals were artificially challenged with *B. microplus* tick larvae on two separate occasions. Cattle with bovine major histocompatibility (BoLA) antigens W6.1 and W7 had significantly fewer ticks than did cattle lacking those antigens. Cattle with BoLA antigens W7 and CA36 had lower concentrations of nematode eggs in their faeces than did cattle lacking these BoLA antigens. The authors concluded that BoLA is one of the genetic systems that influences resistance to *B. microplus*, although it was premature to recommend a role for BoLA in selective breeding to increase tick resistance.

Studies based on gene expression and other methods provide additional supporting evidence of an immunological basis to tick resistance in cattle, although it is similarly premature to recommend evidence from those studies as the basis of a phenotype for the trait. Results from these studies are summarised in Table 2.

Skin hypersensitivity reactions

Acquired tick resistance by cattle is associated with development of a hypersensitivity response to the salivary secretion of the tick. It is manifested by serous exudation and is usually accompanied by a popular reaction at the site of attachment of the tick (Riek 1962). Histological changes in the skin following attachment are also evident, although lesions indicative of an allergic reaction are found only in animals with some degree of resistance. Those changes comprise cellular invasion, predominantly eosinophilic, which extends deep into the dermis (Riek 1962). In highly resistant cattle, blood histamine concentration reached a peak 48 h after infestation with larvae, and subsided to normal levels 7–8 days later, providing additional evidence of a hypersensitivity reaction (Riek 1962). In susceptible cattle, there was little or no variation in histamine concentration during the parasitic life cycle of the tick. In animals with varying degrees of resistance, temporary increases occurred following the larval and nymphal moults (Riek 1962).

The total local concentration of histamine available in the skin is related to resistance, with higher concentrations linked to higher resistance, with detachment of *R. microplus* larvae

Table 2. Studies providing evidence of an immunological basis to tick resistance in cattle

Design	Effect	Source
Comparison of tick-resistant and tick-susceptible breeds	(1) Elevated expression in skin of resistant animals of specific Ca 2^+ signalling genes such as AHNAK, CASQ, IL2, NFAT2CIP and PLCG1 that could be related to host resistance.	Bagnall *et al.* 2009
	(2) Histological studies have shown that cutaneous reactions of resistant hosts to bites of adult ticks had significantly more basophils and eosinophils than did those of the susceptible breed; expression of adhesion molecules, i.e. intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and P-selectin, was higher in adult-infested skin of susceptible hosts undergoing low infestations than in resistant hosts; when the host was exposed to high tick infestations, expression of these adhesion molecules was downregulated in both phenotypes; expression of leukocyte adhesion glycoprotein-1 (LFA-1) was higher in skin from susceptible hosts undergoing low or high infestations than in skin from resistant hosts; conversely, higher levels of E-selectin, which promotes adhesion of memory T-cells, were expressed in skin of resistant animals.	Carvalho *et al.* 2010*a*
	(3) Sequencing of gene coding for heavy chain of IgG2 showed single-nucleotide polymorphisms (SNPs) that generated 13 different haplotypes, 11 of which were novel and five were exclusive in Holstein and three in Nelore breeds; alignment and modelling of coded haplotypes for hinge regions of bovine IgG2 showed differences in distribution of polar and hydrophobic amino acids and in shape, on the basis of distribution of the amino acids; there was also an association between genotypes of the constant region of IgG2 heavy chain and tick phenotypes, suggesting the possibility of certain IgG allotypes hindering function of tick IGBPs.	Carvalho *et al.* 2011
	(4) Examined gene expression and inflammation induced by tick bites in skins of cattle infested with larvae and nymphs of *R. microplus*; also examined expression profiles of genes encoding secreted tick proteins that mediate parasitism in feeding larvae and nymphs; results suggest that allergic contact-like dermatitis develops with ensuing production of IL-6, CXCL-8 and CCL-2 and is sustained by HMGB1, ISG15 and PKR, leading to expression of pro-inflammatory chemokines and cytokines that recruit granulocytes and T lymphocytes, with the response being delayed in susceptible cattle. Transcription data provided insights into tick-mediated activation of basophils; skin from tick-susceptible animals expressed more transcripts encoding enzymes that detoxify tissues; transcripts encoding secreted modulatory molecules by the tick were significantly more abundant in larval and nymphal salivary glands from ticks feeding on susceptible cattle. Genes encoding enzymes producing volatile compounds exhibited significantly lower expression in resistant than in susceptible animals; resistant cattle expose ticks to an earlier inflammatory response, associated with significantly lower expression of genes encoding salivary proteins that suppress host immunity, inflammation and coagulation.	Franzin *et al.* 2017
Comparison of tick-resistant and tick-susceptible animals in an F2 population derived from Gyr (*Bos indicus*) × Holstein (*Bos taurus*)	(1) Microarray data analysis of RNA samples from tick-infested skin was used to evaluate gene expression after *R. microplus* larvae attachment; the differentially expressed genes showed networks and pathways suggesting a key role of lipid metabolism in inflammation control and impairment of tick infestation in resistant animals; the acute-phase response was also impaired in susceptible animals.	Carvalho *et al.* 2014
	(2) Evaluated differences in transcript expression of genes related to immune response in peripheral blood of cattle known to be resistant or susceptible to ticks; gene expression of CD25, IL-10, FoxP3 and CXCL10 was altered in resistant animals at 48 h cf. samples collected before infestation; in susceptible animals, CXCL8 and CXCL10 had altered expression 24 h after infestation. CXCL8 also showed altered expression at 48 h after infestation cf. samples collected before infestation; a correlation was found between T γδ cell activity and the immunological mechanisms, resulting in increased resistance to *R. microplus* in cattle.	Domingues *et al.* 2014

Continued on next page

Table 2. (*continued*)

Design	Effect	Source
Susceptible and resistant tropically adapted taurine animals	Assessed abundance of proteins and mRNAs in skin adjacent to tick-bite sites; results showed substantially higher expression of basal epidermal keratins KRT5 and KRT14, the lipid-processing protein, lipocalin 9 (LCN9), the epidermal barrier catalysing enzyme transglutaminase 1 (TGM1), and the transcriptional regulator B lymphocyte induced maturation protein 1 (Blimp1) in HR skin; data suggest an essential role of the epidermal permeability barrier in conferring greater resistance of cattle to tick infestation.	Kongsuwan *et al.* 2010
Comparison of resistant *Bos indicus* and susceptible *Bos taurus* breeds	(1) Significant between-breed differences in percentage of cellular subsets comprising the peripheral blood mononuclear cell population, cytokine expression by peripheral blood leukocytes and concentrations of tick-specific immunoglobulin G1 (IgG1) antibodies measured in the peripheral circulation; gene expression results showed that *Bos indicus* animals developed a stabilised T-cell-mediated response to tick infestation shown by cellular profile and leukocyte cytokine spectrum. *Bos taurus* animals demonstrated cellular and gene expression profiles consistent with a sustained innate, inflammatory response to infestation, although high tick-specific IgG1 titres suggest that these animals also developed a T-cell response to infestation.	Piper *et al.* 2009
	(2) Genes involved in inflammatory processes and immune responsiveness to infestation by ticks were upregulated in Holstein–Friesians but not in Brahmans; by contrast, genes encoding constituents of the extracellular matrix were upregulated in Brahmans; Holstein–Friesians displayed a much greater cellular inflammatory response at site of larval attachment than did Brahmans.	Piper *et al.* 2010;
Comparison of artificially infested Santa Gertrudis heifers with tick-free controls	Blood samples were used to measure peripheral immune parameters: haematology, the percentage of cellular subsets comprising the peripheral blood mononuclear cell (PBMC) population, tick-specific IgG_1 and IgG_2 antibody titres, IgG_1 avidity for tick antigens and the ability of PBMC to recognise and proliferate in response to stimulation with tick antigens *in vitro*; tick-susceptible animals developed significantly higher tick-specific IgG_1 antibody titres than did tick-resistant animals; results suggest that heightened antibody response either does not play a role in resistance or might contribute to increased susceptibility to infestation.	Piper *et al.* 2017
Comparison of highly resistant and highly susceptible animals of the same breed	Skin gene expression was studied using a cattle skin-derived cDNA microarray; in total, 214 genes were differentially expressed in response to larval challenge across all animals; 72 genes were upregulated and 76 downregulated 24 h after challenge; genes with significantly altered gene expression levels following tick infestation were predominantly keratin or mitochondrial genes, as well as odorant binding protein (OBP) and *Bos taurus* major allergen BDA20; additionally, 66 genes were found with differential expression between highly resistant and highly susceptible animals at 24 h; of these, genes representing the extracellular matrix and immunoglobulin gene expression pathways were over-represented.	Wang *et al.* 2007
Comparison of the differential regulation of T and B-lymphocyte subsets in the skin and lymph nodes from resistant and susceptible breeds	Skin and lymph nodes were sampled before tick infestation and at larval and adult feeding stages for resistant (Brahman and Bonsmara) and susceptible Holstein–Friesians. Tick-resistant breeds showed significant increases in CD3+ T-lymphocytes and tingible body macrophages. While susceptible breeds showed a decrease followed by an increase in B-lymphocytes after infestation, resistant breeds did not show any fluctuation for CD20+ and CD79a+ B-lymphocytes in lymph nodes. Susceptible animals also showed increased variability in γδ T-lymphocytes in lymph nodes, while resistant animals showed a more stable T helper lymphocyte population. The results suggested that resistant animals are able to modulate B-lymphocyte and WC1+ δσ T-lymphocyte differentiation.	Robbertse *et al*. 2018

precipitated by histamine release (Willadsen *et al.* 1979; Kemp and Bourne 1980). The possibility of using local histamine concentrations in the skin as possible criteria for selection of resistance should be considered, given that biosensors for biogenic amines are becoming feasible (Rong *et al.* 2017).

A recent updated review considering bovine immune factors that underlie tick resistance concluded that the single most important mediator of resistance remains histamine and its associated cell types and molecules (Robbertse *et al.* 2017). It is, therefore, of interest that at least some tick species secrete abundant histamine-binding proteins in their saliva during feeding, and these act as scavengers to inhibit inflammation (Paesen *et al.* 1999; Mans 2005). Ticks with experimentally confirmed histamine-binding activity, histamine-binding proteins or histamine countering activity include the hard ticks (*Amblyomma americanum*, *Dermacentor reticulatus*, *Haemaphysalis spinigera*, *Hyalomma asiaticum*, *R. appendiculatus*, *R. evertsi evertsi* and *R. sanguineus*; Chinery and Ayitey-Smith 1977; Chinery 1981; Neitz *et al.* 1993; Paesen *et al.* 1999; Sangamnatdej *et al.* 2002; Aljamali *et al.* 2003; Wang *et al.* 2016) and the soft ticks (*Argas monolakensis*, *Argas reflexus*, *Ornithodoros savignyi* and *O. turicata*; Mans *et al.* 2008; Neelakanta *et al.* 2018). The histamine-binding proteins belong to the lipocalin family and while some family members may not bind histamine *per se*, they might bind other bioactive molecules involved in the regulation of host defences. Most species probably possess related biogenic amine-binding proteins that scavenge serotonin, an important platelet agonist (Mans *et al.* 2017).

In some cases, such as for the hard tick *Ixodes scapularis*, serotonin-binding but not histamine-binding activity is present in adult tick saliva (Mans *et al.* 2008). In other ticks, histamine-binding proteins have been inferred on the basis of sequence identity, homology or molecular docking experiments (Díaz-Martín *et al.* 2011; Rodriguez-Valle *et al.* 2013; Valdés 2014). However, the results of these studies need to be confirmed experimentally, since it has been indicated that sequence similarity or even the presence of a biogenic amine-binding motif does not guarantee histamine binding (Mans *et al.* 2017). This is especially relevant for ticks such as *R. australis* (previously *R. microplus*), where tick rejection has been associated with an increased histamine concentration at the feeding site (Tatchell and Bennett 1969; Willadsen *et al.* 1979; Kemp and Bourne 1980), suggesting that these ticks do not have significant concentrations of histamine-binding proteins in their saliva. Alternately, histamine-binding proteins may be present in other members of the *R. microplus* complex, and this may be determined only empirically. For the majority of studies, the presence of histamine-binding lipocalins has not been confirmed in larval, nymphal or adult stages. The possibility, therefore, exists that even for ticks that possess histamine-binding proteins, a single life stage may be susceptible to resistant cattle. Also, field responses to resistant cattle may be complex, given that multiple genes with biogenic amine-binding motifs are present in tick transcriptomes and regulation of salivary genes may vary at individual tick level (Mans *et al.* 2017). The choice of tick species, the origin of the tick population and the initial diversity of the tick population may all influence the outcome of genetic selection for resistance.

Riek (1962) also provided some evidence that it might be possible to induce the hypersensitive state, with a consequent reduction in tick burden, by repeated daily subcutaneous injections of 0.5 mL of a 1 in 10 dilution of larval extract. This evidence was subsequently used by Bechara *et al*. (2000) to test the use of unfed larval extract as a measure of tick resistance in a small number of animals. Marufu *et al*. (2013) subsequently used the method described by Bechara *et al*. (2000) in larger numbers of animals, as described in more detail in a later section of this review.

Induction of this hypersensitive state is probably related to acquired immunity and may suggest that other antigens could elicit the hypersensitive response. In this regard, transcriptome studies have indicated a high degree of tick salivary-gland complexity with potentially hundreds to thousands of proteins secreted over the course of a feeding event (Mans 2016; Mans *et al.* 2016). Many of these proteins target central molecules involved in inflammation, blood coagulation and platelet aggregation. Several of them are scavengers of important inflammatory and platelet-aggregation mediators such as thromboxane A_2, an important platelet-aggregation agonist that mediates collagen-induced platelet aggregation (Mans and Ribeiro 2008*a*); leukotriene B_4, an important stimulant of neutrophil migration, aggregation and degranulation (Beaufays *et al.* 2008; Mans and Ribeiro 2008*a*); or the cysteinyl leukotrienes LTC_4, LTD_4 and LTE_4, that induce oedema (Mans and Ribeiro 2008*b*). The complement pathway, specifically C3 or C5, is also targeted by ticks (Ribeiro 1987; Valenzuela *et al*. 2000; Nunn *et al*. 2005; Daix *et al*. 2007; Schroeder *et al*. 2007; Mans and Ribeiro 2008*a*; Schuijt *et al*. 2011; Franco *et al*. 2016; Silva *et al*. 2016). Several chemokine and cytokine inhibitors have also been characterised in ticks (Hajnická *et al.* 2001; Vančová *et al.* 2007, 2010; Frauenschuh *et al.* 2007; Déruaz *et al.* 2008; Bonvin *et al.* 2016; Hayward *et al.* 2017). Most ticks also possess apyrase that hydrolyses ADP, a platelet-aggregation agonist, and ATP, a pro-inflammatory molecule (Mans 2016). In addition, most tick species possess at least a thrombin inhibitor or possibly even more than one inhibitor of the clotting cascade (Mans *et al.* 2016). The number of inhibitors are not surprising since inflammation, the complement cascade, blood clotting and platelet aggregation are not independent processes, but comprise an interdependent and highly integrated defence mechanism requiring a multi-targeted attack by the tick (Mans 2016). The ability of ticks to modulate the host's immune system is, therefore, much more advanced and complex, suggesting that resistance in cattle may be multifactorial.

In addition to this hypersensitivity reaction, Carvalho *et al*. (2010*b*) showed that, relative to normal skin, cattle that are genetically susceptible to tick infestations have an increased clotting time of blood collected from the immediate vicinity of haemorrhagic feeding pools in skin infested with different developmental stages of the tick. Conversely, the clotting time of tick-infested skin from genetically resistant cattle was shorter than that of normal skin. Their data indicated that ticks are able to modulate their host's local haemostatic reactions. In the resistant phenotype, larger numbers of inflammatory cells (eosinophils and basophils) were recruited and the authors speculated that increased tissue factor levels due to elevated eosinophils might

result in greater coagulation (Carvalho *et al*. 2010*b*). The authors also suggested that resistant hosts may downregulate the expression of anti-haemostatics in tick salivary glands. More recently, the same approach was repeated and similar trends were observed (Franzin *et al.* 2017; Maruyama *et al.* 2017). The possibility that resistant hosts may manipulate tick expression patterns is an exciting observation with regard to selection of resistant breeds. This phenotype (downregulation of tick expression) may also be considered as a potential criterion for genetic improvement of tick resistance.

Volatile semiochemicals

Locating of vertebrate hosts by ectoparasitic insects (flies) and acarines (ticks, mites) is mediated by several different stimuli emanating from the host, including visual cues (size, skin colour and pattern), heat, carbon dioxide and volatile organic compounds. The latter, which are known to play a major role in vertebrate–ectoparasite interactions, are detected by olfactory organs located in the peripheral nervous system of the ectoparasites, e.g. insect antennae. Manipulation of these behaviour-modifying chemical signals, otherwise known as semiochemicals, has long been viewed as a target for practical development of new interventions against ectoparasite pests that exhibit nuisance behaviour and can transmit causative agents of infectious diseases (Logan and Birkett 2007).

Gothe (1987) and Sonenshine (2004, 2006) each reviewed the role of semiochemicals in mediating important aspects of tick behaviour. These information-containing compounds include pheromones (used for conspecific communication), allomones (defence secretions) and kairomones (used for host identification and location). Pheromones, the best known and most intensively studied of these semiochemicals, include arrestment (assembly) pheromones, attraction–aggregation–attachment pheromones and sex pheromones. Ticks also produce an allomone that protects against some insect predators. Ticks use kairomones for host identification, including, for example, volatiles such as CO_2 and NH_3 and various oils such as glandular secretions from the host. Over the past 10–20 years, knowledge of different tick pheromones, allomones and kairomones has been used to develop novel tick-control products by incorporating tick pheromones and small amounts of pesticide to attract and kill ticks on their hosts or in vegetation (see Latha (2012), for a detailed summary of these various uses of semiochemicals). However, rather than using the semiochemicals for the production of anti-tick treatments, our interest is in exploring the possibility of quantifying semiochemical production by hosts, to examine whether those concentrations are related to different levels of host resistance to ticks and, hence, could be used as an alternative phenotype for assessing host tick resistance.

The interest in quantifying host-derived semiochemical production stems from earlier research in disease-transmitting cattle flies and dairy cattle in the Netherlands and Denmark. For example, Holstein–Friesian heifers can be ranked according to fly load, and retain their rankings across years, with some heifers consistently attracting flies, whereas others in the same herd carry only a few flies (Jensen *et al.* 2004). In addition, that study demonstrated that it was possible to manipulate overall fly loads in herds to increase or decrease fly numbers by removing or adding susceptible or resistant heifers to the different herds, clearly suggesting a genetic basis to resistance or susceptibility to flies. This finding is in line with the low to moderate estimates of heritability for resistance of cattle to buffalo flies (*Haematobia irritans exigua*) in northern Australia (Burrow 2014), with buffalo flies being similar to the fly species tested in these European studies. Subsequently, Birkett *et al*. (2004) used data from the Jensen *et al*. (2004) study to test the hypothesis that natural differential attractiveness for cattle flies in Holstein–Friesian cattle is partly due to differences in volatile semiochemicals emitted by the host. Coupled gas chromatography–electrophysiology (GC–EAG), coupled gas chromatography–mass spectrometry (GC–MS), electrophysiology (EAG), laboratory behaviour and field studies were used. In volatile cattle extracts collected by air entrainment, several active peaks were located by coupled GC–EAG for two different fly species, namely, *Musca autumnalis* and *Haematobia irritans*. Further collection and testing of different volatile compounds showed that only some of the compounds were physiologically active across the range of flies tested. In field studies using small herds of heifers ranked on their fly load, individual slow-release formulations of 6-methyl-5-hepten-2-one (MHO), when applied to low and high fly-ranked heifers, reduced fly loads on those individuals. The authors concluded that natural differential attractiveness for cattle flies in Holstein–Friesian cattle was due to enhanced production of MHO as a non-host semiochemical in fly-resistant cattle, and suggested that the phenomenon would be likely to also apply to other vertebrate host species and their associated insect pests. The hypothesis of differential volatile signalling for ectoparasites has also been tested for the interaction between humans and mosquitos and biting midges, with results showing that MHO, together with a second compound (geranylacetone) accounts for reduced attractiveness of less-bitten people (Logan *et al.* 2008, 2009). The researchers have, subsequently, hypothesised that the differential volatile signalling in vertebrates derives from oxidative biochemical cleavage of steroidal compounds at the skin surface (M. A. Birkett, pers. comm.). Pertinent to the present review, the hypothesis of differential host signalling has, subsequently, been tested in tick populations in resistant Girolando and Nelore (both *Bos indicus*) and susceptible Holstein (*Bos taurus*) cattle in Brazil, with the study demonstrating that more resistant animals produce greater amounts of MHO plus other ‘repellent’ molecules (M. A. Birkett, pers. comm.). Similar results have been reported for differential attractiveness of different dog breeds to ticks (Borges *et al.* 2015; de Oliveira Filho *et al.* 2016, 2017), with the same hypothesis of differential volatile signalling testing true, albeit the repellents that were identified were different from those in cattle.

While the identification of compounds such as MHO represents the discovery of new repellents for livestock protection against ectoparasites, their use as repellent sprays, such as, for example, pour-ons and eartags, is not sustainable because of technical difficulties with formulations (high volatility causing reduced efficacy). Hence, the long-term aim of this research is to breed animals to produce enhanced

concentrations of the volatile compound that confers resistance to flies (M. A. Birkett, pers. comm.). Further development of the approach might enable the genetics for volatile-repellent production to be defined. This may provide an entirely new opportunity to breed animals for volatile-based resistance, either as a new trait or in conjunction with a more cost-effective method of phenotyping ticks that would potentially improve resistance of cattle for ticks and also biting flies.

Possible new phenotypes for cattle tick resistance

As summarised in earlier sections of the present paper, genetic variation in host resistance is reflected in several different aspects of tick development. However, the early literature was unequivocal that the most important measure was the total count of replete female ticks (i.e. engorging *Rhipicephalus microplus* ticks between 4.5 mm and 8 mm in size). Since total tick counts are affected by a large number of factors (summarised in Table 1), the only reliable comparisons will be those made under contemporary conditions, as suggested in the following practical guide based on infestation with *R. microplus* (Burrow 1997), noting that different guidelines may be required for other tick species:

- Cattle should be managed together as a single management group without dipping to control ticks for at least 6 months before tick assessment.
- Cattle should have had sufficient exposure to ticks to have acquired immunity. On the basis of data from Belmont Research Station in north-eastern Australia, animals need continuous low-level infestations of ticks for a period of ~3 months before tick counts stabilise and animals are considered to have acquired resistance. If tick counts on all animals are very high, it is likely that the animals are still acquiring resistance and if tick counts on all animals are very low, it is likely that there is insufficient tick challenge to measure resistance. As a guide, there should be an average tick count of at least 20 ticks per side of each animal, averaged over at least 15 animals. If the average count is <20 ticks, then the level of infestation is too low to accurately determine tick resistance and an artificial infestation may be necessary. Once resistance to ticks has been acquired, tick resistance is stable across time.
- Animals to be compared must be of a similar age and sex class, i.e. steers should not be compared with bulls, young cattle should not be compared with older cattle, and lactating cows should not be compared with non-lactating cows. Similarly, tick counts on animals from one paddock should not be compared with tick counts on animals from another paddock, even if the paddocks are adjacent, because environmental factors (e.g. previous stocking rates) are likely to affect the tick populations in the different paddocks.
- Nutritional stress should be minimised at the time of assessment because animals undergoing nutritional stress often demonstrate an impaired immune system.

As suggested above, development and validation of a new phenotype(s) for tick resistance should initially be undertaken using the cattle-management guidelines above, with half-body tick counts as the standard against which any new phenotype(s) are compared. Options that could be considered as the basis of a new tick-resistance phenotype(s) could include technological approaches to counting ticks (e.g. high-resolution imagery in combination with electronic animal identification and sensor networks), use of clinical signs of cattle susceptibility to ticks (e.g. anaemia and decreased immune function and obvious hide and udder damage), measures of hypersensitive skin reactions, or animal behavioural assessments (e.g. amount of movement with more lethargic animals possibly also being those with greater susceptibility to ticks).

Measures of haematological parameters

The first possible new phenotype considered is development or modification of a method used by Andronicos *et al*. (2014) to examine relationships between haematological parameters and the ability of sheep to resist infection with the parasitic nematode *Haemonchus contortus*. In their study, blood samples from individual sheep that had been challenged by worms earlier in their lives were analysed for a standard haematological panel. The blood parameters measured were haematological (including red blood cell count, haematocrit, haemoglobin concentration), as well as immunological (including numbers of eosinophils, basophils, neutrophils and monocytes). Thereafter, a multivariate analytical approach was used to define algorithms on the basis of the combined blood parameters to rank the ability of sheep to resist nematode infection, in a single blood sample. The algorithms were shown to classify susceptible sheep with 100% accuracy and resistant sheep with 80% accuracy. However, no attempt was made to evaluate the resistance or susceptibility of individual animals, as only representative animals from extreme lines were tested. The novelty of this approach was the use of multivariate models of analysis and a machine-learning approach to combine all of the blood parameters relative to the traditional approach of examining each parameter on a case-by-case basis.

Subsequent experiments by this same research group (Bell *et al*. 2019) applied this multivariate approach to large flocks of outbred sheep (i.e. animals not previously selected for parasite resistance or susceptibility). Initially, blood parameters were measured in animals under an artificial worm challenge, and the data were used to derive a regression model defining the relationship between the level of worm infection and the various blood parameters. This model was then applied to data collected from a second experiment where animals acquired natural worm infections in the field over a period of several months. The ability of the model to predict the worm-infection status of individual animals was assessed by comparing model predictions with actual infection levels at the end of the experimental period. Approximately 65% of the cohort of animals that were most susceptible to worm infection (highest worm-egg counts) were predicted to be susceptible on the basis of the haematology-based model.

The biological basis of the worm resistance test described by Andronicos *et al*. (2014) is presumed to lie in the following two aspects of the interaction of *H. contortus* with their sheep host: first, the blood-feeding habit of this worm species that results in anaemia in infected animals; and second, the role of leukocytes in the host response to nematode infection. Eosinophils, mast cells, basophils and neutrophils have been implicated in the immune response to helminths (Anthony *et al.* 2007; Voehringer 2011;

Allen *et al.* 2015). In general terms, the interaction of ticks with their host animals involves both these aspects seen with blood-feeding helminths, i.e. anaemia and the involvement of leukocyte cell types, including eosinophils, basophils and mast cells in the immune response (Wikel 1996; Brossard and Wikel 1997; Jonsson *et al.* 2014). This general level of concordance between the two host–parasite interactions, combined with the novelty of multivariate analysis and machine-learning approaches to derive algorithms to relate infection levels to blood parameters, provides the rationale behind our suggestion that the approach of Andronicos *et al*. (2014) may be applicable to tick-resistance phenotyping.

A limitation of this approach is that the use of haematological parameters to predict parasite-resistance status, either specifically for worms or ticks, will need to operate under conditions of co-infection with other parasites or diseases. In some cases, where a phenotypic test for tick resistance may be required, the animals may also be affected by tick-borne disease (bacterial or protozoan) or parasitic worms. Ticks at different life stages will also likely be present. However, it is possible that the different feeding habits of the various parasites (e.g. blood-feeding of ticks versus mucosal grazing of many worm species), as well as the different generalised immune response (Type 1 helper T-cell for protozoa and bacteria vs Type 2 for worms and ticks), will result in different 'signatures' of response as defined by a regression model derived from all the red and white blood cell parameters. Testing of this will require comparisons of controlled experiments (tick infections only) with co-infection studies. The usefulness of a haematological tick-phenotype test will depend on the regression model being able to show a degree of specificity in accounting for tick-mediated effects as distinct from the effects of the other potential infections. Advantages and disadvantages of this possible phenotype are summarised in Table 3.

Measures of skin hypersensitivity reactions

A second possible new phenotype is based on the skin hypersensitivity reaction described previously. Bechara *et al*. (2000) used measurements of skin hypersensitivity to correlate host resistance to ticks in 20 *Bos indicus* and *Bos taurus* (10 of each breed type) animals. The method was subsequently used by Marufu *et al*. (2013, 2014) to distinguish levels of tick resistance in larger numbers of Nguni and Bonsmara heifers. The test used by these studies is based on the reaction elicited by intradermal inoculation of 0.1 mL unfed larval extract from the tick in the animal's ear. Ear thickness is measured using callipers before and after inoculation.

The process to derive the unfed larval extract requires skilled laboratory technicians, with unfed tick larvae (2 months old) from a laboratory colony of ticks killed by immersion in liquid nitrogen, homogenised with a ground glass homogeniser in phosphate buffered saline (PBS, pH 7.4) and sonicated three times for 10 s each and once for 60 s (20 MHz). The extract is then centrifuged at 12 000*g* (4°C) for 1 h and the supernatant filtered through a 0.22-μm Millex-GV (Millipore) filter and stored at −40°C until use.

Thereafter, animals are given a 0.1-mL intradermal injection (50 μg of protein) of the larval extract in a shaved area on the outer surface of the left ear. An equal volume of PBS, pH 7.4, is inoculated in the contralateral ear to provide a control. Ear thickness is measured in triplicate with the aid of a Mitutoyo® precision instrument just before the injection and at various times post-inoculation. Results are expressed as the percentage of increase in ear thickness compared with the initial measurement. Values obtained from PBS-injected ears are subtracted from those for unfed larval extract-injected ears (Marufu *et al*. 2013).

In the Bechara *et al*. (2000) study, *Bos taurus* calves with acquired tick resistance showed an immediate reaction with maximum response (75% increase in ear thickness) at 10-min post-inoculation. Resistant *Bos indicus* calves presented an immediate response with maximum reaction (70% increase in ear thickness) between 10 min and 1 h post-inoculation.

However, Marufu *et al*. (2013) indicated that Bonsmara cattle showed a more intense immediate reaction and no delayed hypersensitivity reaction to larval extracts of *Rhipicephalus* ticks, whereas Nguni heifers presented a less intense

Table 3. Advantages and disadvantages of the haematological analysis as a new phenotype

Advantage	Disadvantage
• If blood is being collected for parentage or genotyping purposes, this phenotype provides multiple usage for a single intervention, provided the blood collection occurs after the animals have acquired resistance to ticks	• The ability of the regression models to distinguish between infections with ticks and bacterial, protozoan or helminth infections will need to be tested under controlled experimental conditions
• Potentially offers same-day results, providing information for management decisions, in addition to data for genetic improvement	• A portable haemolytic analyser would need to be purchased, probably by a service provider who would then travel to the farms to undertake assessments (i.e. timing of assessments would be determined by availability of a service provider)
• Multivariate cf. univariate analysis improves the repeatability of the measurement	• Additional research is required to use the mathematical functions derived in this method to rank an animal's ability to resist parasite infection on the continuum of resistance in the population as a whole (rather than just classifying animals as 'resistant' or 'susceptible')
• The machine-learning approach enables continuous improvement of the algorithms	• May need to develop decision-support tools to enable interpretation of results relative to herd averages, to improve the prediction accuracy or to use the results for management purposes
• Non-linear relationships (e.g. threshold responses) can be accommodated for management purposes	• Validation of the approach for use in cattle tick resistance and in industry herds would be required
• Offers strong potential to overcome the limitations of accurate phenotypes for traits where the impacts reflect immune function or anaemia (as in host tick resistance)	

Table 4. Advantages and disadvantages of the skin-hypersensitivity phenotype

Advantage	Disadvantage
• After animals have acquired their resistance to ticks, the phenotype may be able to be recorded at a single point in time, independent of the current tick-infestation status • Possibly offers same-day results (pending resolution of questions around timing of measurements across different breed types and tick species), which would allow same-day management decisions, in addition to data for genetic improvement • Non-linear relationships (e.g. threshold responses) should also be able to be accommodated for management purposes	• Achieving unfed larval-extract inoculants requires specialist technical expertise and laboratory facilities • A service provider would be needed to undertake inoculation, meaning that the timing of tick-resistance assessments would be determined by availability of a service provider • Additional research is required to evaluate the reaction times for a broader range of breed types and for relevant tick species • May need to develop decision-support tools to enable interpretation of results relative to herd averages, to improve the prediction accuracy or to use the results for management purposes • Validation of the approach for use in industry herds would be required

immediate reaction and a delayed hypersensitivity reaction at 72 h post-inoculation with larval extracts of the same tick species. Reactions to *R. decoloratus* larval extract produced a more intense skin response at all time intervals in both breeds than did that to *R. microplus*. These results indicate that additional research is needed to identify the best time of measurement of the hypersensitivity reaction across different breed types and different tick species. In addition, for further development of the hypersensitivity phenotype per sé, consideration could also be given to the possible use of infrared thermography with a portable device (e.g. phone or tablet) and development of an 'app' to measure skin responses to inoculation with larval extracts as an alternative to measurements of skin thickness. Advantages and disadvantages of this possible phenotype are summarised in Table 4.

Simplified artificial tick infestation ('tick-bag test')

As outlined above, artificial tick infestations have been used for several decades to assess cattle resistance to ticks when insufficient variation in tick numbers occurs during natural infestations. Artificial infestations overcome the problem of seasonal variation in tick numbers, but generate their own disadvantages, such as, for example, the need for tick-breeding facilities and skilled laboratory technicians to deliver the tick larvae for use on-farm, the strong likelihood of infesting pastures with ticks, thereby exacerbating the tick problem, and a need to muster animals on at least two occasions to assess animal resistance to ticks.

A simplified test (referred to here as the 'tick-bag test') was developed by Heyne *et al*. (1987) to overcome at least one of those disadvantages, i.e. contamination of pastures with ticks. The test involves the following: (1) restraining the animals in a crush to enable a circular part of their upper back to be shaved for easier attachment of ticks (although for assessments of host resistance to ticks, this may not be ideal as it does not replicate the conditions ticks would encounter when animals are grazing); (2) a calico bag (Fig. 2) is attached to the clean-shaven area using a contact adhesive applied to the outer ring, followed by a 24-h drying period; (3) a specified number of tick larvae (estimated by weight of larvae) are placed into opened plastic vials (to allow the ticks to exit), which are then inserted into the calico bags before the bag is twisted shut and secured with a rubber castration ring; and (4) the bags are monitored twice daily until larvae are ready for counting (e.g. Days 18–21 for the *Rhipicephalus* spp.) following removal of the bags.

Fig. 2. Application of the 'tick bag' artificial tick-infestation method.

The test was developed specifically to facilitate evaluation of the transmission of diseases by ticks and, subsequently, to test efficacy of chemicals to control tick infestations in many different animal species, but with no attempt made as yet to determine its role in evaluating individual host resistance to ticks. If the test is to be useful for phenotyping animals for their resistance to ticks, genetic correlations will need to be estimated between the test- and individual-animal tick counts to establish the test as a reliable indicator of tick resistance. Consideration may also need to be given to the species of tick larvae used in the test and whether the larval composition is representative of natural tick infestations in the region. There are no known published reports indicating the magnitude and direction of either phenotypic or genetic correlations between half- or whole-body tick counts and results from the tick-bag test.

Table 5. Advantages and disadvantages of simplified tick infestations using adhesive calico bags

Advantage	Disadvantage
• The tick counting process is simplified or possibly can be replaced by weighing the ticks (comprising dead larvae in resistant animals through to fully engorged ticks in susceptible animals) • The number of ticks potentially infesting the cattle is known, assuming that can be considered a genuine measure of host resistance to ticks • Ticks are fully enclosed within the bag, which means that pastures are not infested when fully engorged females drop from the animal to lay their eggs • Tick larvae can be guaranteed not to transmit diseases to the cattle • Treatment of cattle using acaricides at the end of the infestation period ensures that animals are free of ticks following tick-resistance assessment	• Accessing tick larvae requires specialist technical expertise and laboratory facilities • A service provider would likely be needed to undertake artificial infestation, meaning that the timing of tick-resistance assessments would be determined by availability of a service provider • Animals need to be retained in facilities for close checking of the bag (1 or 2 times per day) over the period while ticks mature (up to 21 days for *R. microplus*), so as to ensure that the bags have not been dislodged; this requirement would preclude the ability of animals to graze at pasture during assessments (as is the case in nucleus and commercial seedstock herds aiming to evaluate animals for their resistance to ticks) • If new research can ensure that the test is sufficiently robust to enable cattle to graze at pasture over the tick-assessment period, there will still be a need to muster animals on at least two occasions to infest and then count the animals. Under extensive pastoral systems, mustering is often a significant expense in its own right • In regions where multiple tick species infest cattle, it is unlikely that the ticks included in the bags would be representative of the mix of tick species under natural tick infestations • Validation of the approach for use in industry herds would be required

Advantages and disadvantages of this possible phenotype are summarised in Table 5.

Measures of semiochemicals

As outlined above, determining whether a relationship exists between tick counts and levels of semiochemicals is regarded as a strongly synergistic opportunity to investigate the possibility of developing an entirely novel trait (volatile-based resistance), with potential to improve cattle resistance to several ectoparasites such as ticks and biting flies. While measurement of semiochemicals using current methods does not satisfy the desirable features of a new phenotype for tick resistance suggested earlier, it is recommended that any research program established to evaluate alternative measures of tick resistance in cattle should include measures of the volatile chemistry of those animals. Should the volatile-based resistance phenotype prove to be useful for genetic-improvement programs, then it would also be necessary to identify more practical ways of assessing volatile-based resistance in commercial and smallholder herds. Thus, consideration should also be given, during the design of any research program, to inclusion of potentially simpler measures that might be correlated with volatile-based resistance to evaluate the phenotype, so as to enable those correlations to also be tested.

Other possible phenotypes for tick resistance

There are several additional potential phenotypes for tick resistance that could be considered for development and testing using high-resolution imagery (digital and infrared) based on different data-capture methods (such as e.g. in conjunction with walk-over weighing or similar 'self-measurement' technologies, use of drones), in conjunction with mobile data-acquisition systems such as sensor networks. It may also be possible to remotely monitor animal-behaviour patterns to determine whether, for example, the amount of movement or rubbing or grooming behaviours are associated with the degree of tick infestation on individual animals. Recent studies in Brazil investigated the use of low-resolution infrared images to detect ticks in cattle, as well as introducing a new automatic method to analyse the images and count the ticks captured in the images (McManus *et al.* 2016; Barbedo *et al.* 2017). However, the authors suggested that the infrared thermographic images have limited potential for detecting ticks in cattle because they enable just a rough estimate for the degree of infestations. However, their algorithm was able to emulate the visual estimates using the infrared thermal images 'reasonably well', suggesting that improvements in the image capture should increase the accuracies for automatic counting (Barbedo *et al.* 2017). In addition to these phenotypes, measurement of skin histamine concentration, or downregulation of tick salivary-gland expression may also be considered in future.

Once phenotype(s) correlated with the 'gold-standard' tick counts have been validated, it is expected that those new phenotype(s) will then be incorporated into new '-omics' studies (e.g. functional genomics, gene expression, transcriptomics, proteomics and metabolomics, along the lines of the results summarised in Table 2) to identify more precisely cattle that are either resistant or susceptible to ticks, potentially enabling simpler and more cost-effective diagnostic tests.

Recent advances in genomic sciences are now also providing unique opportunities to survey microbial communities, especially in various living organisms. These relationships (e.g. symbiotic, commensal or parasitic) have evolved to drive important and measurable phenotypes such as disease susceptibility, for example Ruiz-Rodríguez *et al.* (2009) and Pearce *et al.* (2017). Microbial communities characterised from the skin, gut, vagina and other parts of humans, animals and birds have shown interesting genetic variations linked to distinct

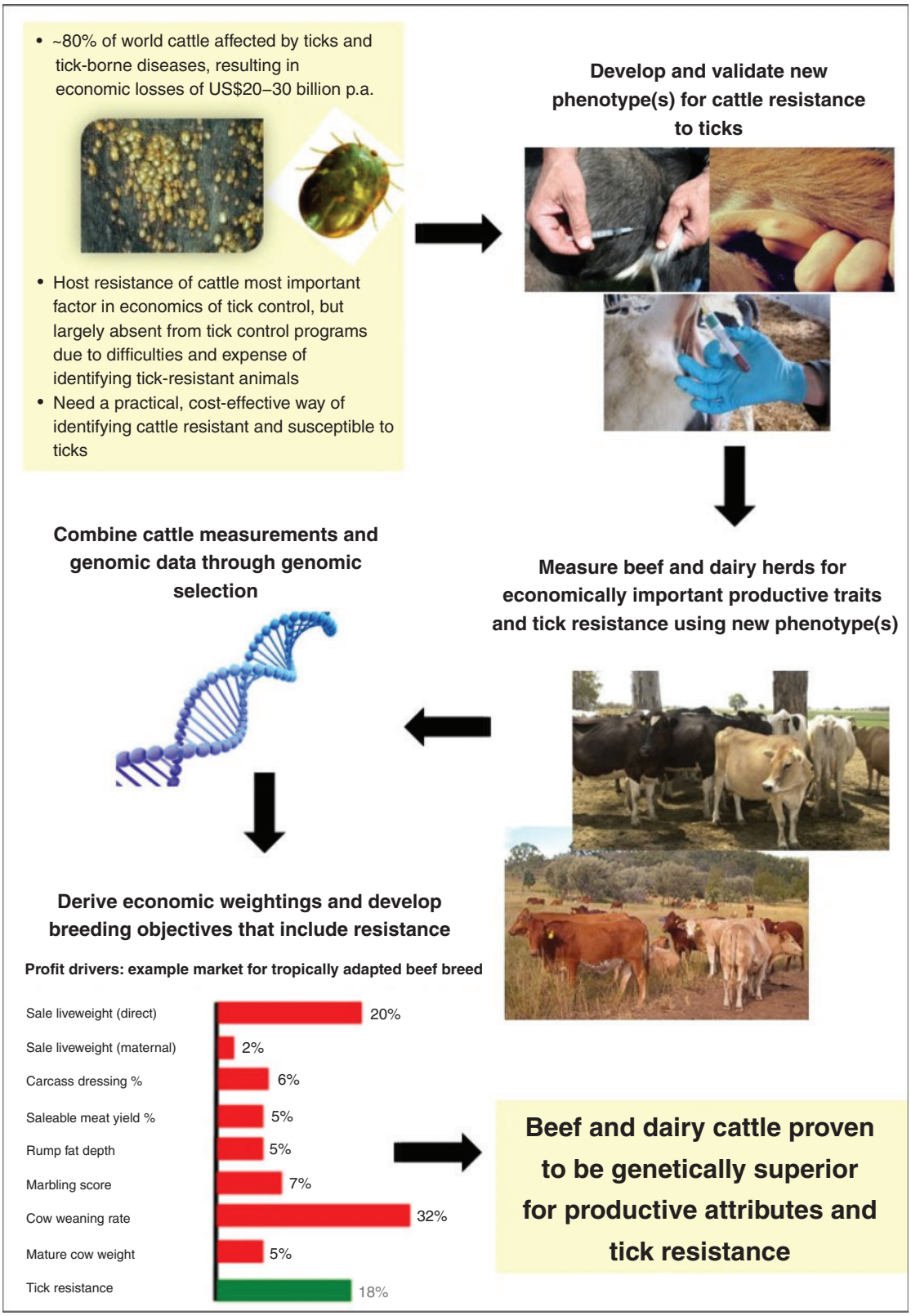

Fig. 3. Steps in the application of practical and cost-effective phenotype(s) for tick resistance in beef and dairy cattle in tropical and subtropical regions globally.

phenotypic outcomes. As the field of livestock microbiome-community study emerges, it will be opportunistic to consider studies of microbiome communities (on the skin and parts of the bodies) to further detect and dissect heritable variations of cattle to resistance to tick infestations. Embarking on metagenomics to support quantitative and qualitative analyses of tick communities on cattle that display differences in tick resistance will be most likely to provide additional options for novel phenotyping methods.

Regardless of the potential of any of these technologies, currently all of these approaches fail with regard to some of the desirable features of a new phenotype outlined previously. While all are potentially capable of being applied under extensive pastoral production systems if the systems can be developed sufficiently well to reliably assess the number of ticks on a particular site(s) of the animal (and potentially distinguish among different tick species if that is identified as being important), none satisfies the requirement of being able to determine the level of acquired host tick resistance when tick infestations are low. Hence, these technologies should continue to be considered, but they are not included in the recommendations for developing and validating new phenotypes in the following section.

Assuming that it is possible to develop and validate new phenotype(s) for host tick resistance, application in beef and dairy cattle-resource populations in tropical and subtropical areas of the world would follow a pathway similar to that shown diagrammatically in Fig. 3.

Recommendations

On the basis of the present review, it is recommended that three potential new phenotypes (same-day haemolytic analysis; same-day measures of skin hypersensitivity reactions; and artificial infestations using the 'tick bag') be investigated and further developed to determine their practical feasibility for consistently, cost-effectively and reliably measuring cattle tick resistance in thousands of individual animals in commercial and smallholder farmer herds in tropical and subtropical areas globally. During evaluation of these potential new phenotypes for tick resistance, additional measurements should be included in any experimental protocol to determine the possibility of developing a volatile-based resistance phenotype to simultaneously improve cattle resistance to both ticks and biting flies. Because the current measurements of volatile chemistry do not satisfy the requirements of a simple, cost-effective phenotype for use in commercial cattle herds, consideration should also be given to inclusion of potentially simpler measures that might enable indirect selection for volatile-based resistance.

We propose that the best method to incorporate all populations, novel phenotypes and gold-standard phenotypes to produce the most accurate genomic predictions for tick resistance is a multi-trait genomic restricted maximum-likelihood approach (G-REML; Maier *et al.* 2015; Hayes *et al.* 2017). In this approach, each phenotype and phenotype × population (where populations can even be in different countries, as demonstrated by Hayes *et al.* 2017) is treated as a separate trait. Genetic (or genomic) correlations are estimated among the traits, and among the populations, provided there is sufficient genomic relationship between them (in human studies, elements of the genomic relationship between pairs of individuals can be as low as 0.025 and still contribute information; Maier *et al.* 2015). The multiple-trait G-REML approach has the advantage that genomic predictions for all individuals are made on the 'gold-standard' trait scale, with the novel phenotypes contributing accuracy to these phenotypes according to the genetic correlations.

The sample size required for accurate genomic predictions (of non-phenotyped individuals) is:

$$r = \sqrt{\frac{Nh^2}{Nh^2 + M_e}}$$

where r is the accuracy of genomic prediction, N is the number of individuals genotyped and phenotyped, h^2 is the heritability of the trait, and M_e is the number of independent chromosome segments, which is $\sim 2N_eL$, where N_e is the effective population size and L is the length of the genome in Morgans (Hayes *et al.* 2009). This equation implies that thousands of animals must be phenotyped and genotyped to enable accurate genomic predictions of tick resistance, given moderate to low h^2, and large N_e for tropical cattle populations. Using this formula and an estimated h^2 of 0.19, Reis *et al.* (2017) indicated that sample sizes of 20 870 and 28 939 animals would be required to achieve a 0.90 accuracy for tick-resistance genomic prediction for Hereford and Braford cattle respectively, in Brazil. Using this multiple-trait approach, all available data can be combined across traits and across countries to achieve the required accuracy for reliable predictions.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

This review was undertaken to inform an international workshop organised as part of a Global Challenges Research Fund Impact Accelerator Award through the Roslin Institute and the Centre for Tropical Livestock Genetics and Health (CTLGH) at the University of Edinburgh, UK. Sincere thanks are due to the Roslin Institute for partial funding of the research and to staff of the CTLGH and the Agricultural Research Council in South Africa for their assistance with organisation of the international workshop held in South Africa in December 2017. The research was also partially funded by the Bill and Melinda Gates Foundation, with UK aid from the UK Government's Department for International Development (Grant Agreement OPP1127286) under the auspices of the Centre for Tropical Livestock Genetics and Health (CTLGH), established jointly by the University of Edinburgh, SRUC (Scotland's Rural College), and the International Livestock Research Institute. The findings and conclusions contained herein are those of the authors and do not necessarily reflect positions or policies of the Bill and Melinda Gates Foundation nor the UK Government.

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